REMARKS

The claimed invention relates to the identification and use of diagnostic markers for distinguishing amongst a plurality of cardiovascular disorders. The present claims refer to methods that comprise assaying a sample for the presence or amount of one or more subject-derived markers related to blood pressure regulation, and for the presence or amount of one or more subject-derived markers related to myocardial injury, and characterizing the subject's risk of having developed or of developing each cardiovascular disorder based upon the presence or amount of the markers measured. As described in detail in the specification, in certain embodiments, this characterization is performed without comparing the amount of one or more of the markers measured to a predetermined threshold amount.

Claims 1-17, 37, and 38 are presently pending in the application.

Applicants note that claims 37 and 38, which are directed to subject matter that the Examiner acknowledges is enabled by the present specification (Office Action, page 7, last paragraph), have not been examined on their merits. Applicants respectfully request that the finality of the office action be removed and these claims be examined or, in the alternative, that the Examiner indicate that claims 37 and 38 are allowable.

Applicants expressly reserve the right to claim subject matter not yet or no longer claimed in one or more applications that may claim priority hereto. Applicants respectfully request reconsideration of the claimed invention in view of the following remarks.

1. Rejection of claims 1-10, 13, and 15-17 under 35 U.S.C. § 112, first paragraph (written description)

Applicants respectfully traverse the rejection of claims 1-10, 13, and 15-17 as allegedly failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

Claim 1 refers to a method of analyzing a subject sample for a plurality of subject-derived markers selected to distinguish amongst a plurality of cardiovascular disorders. These methods comprise assaying the sample for the presence or amount of one or more subject-derived markers related to blood pressure regulation, and for the presence or amount of one or more subject-derived markers related to myocardial injury. Based upon the presence or amount of the markers measured,

the results of the assays performed are used to characterize the subject's risk of having developed or of developing the plurality of cardiovascular disorders.

The Examiner continues to focus on the number of possible markers that might be used in performing the claimed method without any context provided by either the specification or the knowledge available to one of skill in the art. The skilled artisan understands that each marker class referred to in the claims describes markers related to one another by their common relationship to a well known and specified physiological pathway. The simple fact is, the fact that a large number of suitable markers are known in the art to be related to myocardial injury, blood pressure regulation, *etc.* is hardly evidence of failure to comply with the written description requirement. Instead, it is evidence that the skilled artisan has knowledge of an enormous number of such markers, and nothing of record would suggest to the skilled artisan that any and all of these markers could find use in the present invention.

For example, a subject-derived marker "related to myocardial injury" as that term is used in the art refers to certain detectable macromolecules that are expressed by the cells of a subject, the levels of which are related to the presence of a myocardial injury. Members of this marker class have long been well known in the art, and the specification describes numerous other markers that are also known in the art to be markers for ruling in or out myocardial injury. These include cardiac troponin T, annexin V, β-enolase, CK-MB, glycogen phosphorylase BB, heart type fatty acid binding protein, and S-100ao. The examples provided in the present specification are not exhaustive. For example, Table 4 of U.S. Patent 5,710,008, cited by the Examiner in an obviousness rejection, refers to many additional markers said to be useful for this purpose. Moreover, Kemp *et al.*, *Br. J. Anaesthesia* 93: 63-73, 2004, notes that the first account of the use of biochemical markers related to myocardial injury was published in 1954, and lists 14 known biomarkers for this purpose. *See, e.g.*, Kemp *et al.* page 65, Table 2. And U.S. Patent 5,290,678 states in column 8, lines 16-38, that myocardial injury may be identified using virtually any cardiac proteins.

Likewise, a subject-derived marker "related to blood pressure regulation" is a detectable macromolecule that is expressed by the cells of a subject and that has a relationship with blood pressure regulation. The specification provides numerous examples of this category of markers, including natriuretic peptides such as BNP. Such markers are known in the art to play a "key role in

salt and water homeostasis and blood pressure regulation through direct vasodilator, diuretic, and natriuretic properties." Freitag *et al., Hypertension* 41: 978-83 (2003). Similarly, a subject-derived marker "related to inflammation" is a detectable macromolecule that is expressed by the cells of a subject and that has a relationship with inflammation. This category of marker is well known and well studied in the art. *See, e.g.*, Biasucci, *Circulation* 110: e560-e567, 2004. The present specification again provides numerous examples of such markers. And a subject-derived marker "related to coagulation and hemostasis" is a detectable macromolecule that is expressed by the cells of a subject and that has a relationship with coagulation and arresting of bleeding ("hemostasis"). As is well known in the art, such markers "allow the detection of *in vivo* coagulation activation." Fassbender *et al., Stroke* 30: 2101-4 (1999). And again, the specification provides numerous examples of this category of markers.

As demonstrated by the articles cited in the preceding paragraph, Applicants note that there is nothing unusual in the art with regard to referring to these biomarkers generally by reference to their art-recognized classes, particularly in the diagnostic arts. Reference to art recognized classes of biomarkers also is reflected in issued U.S. Patents. *See, e.g.*, U.S. Patent No. 5,604,105, which refers to a method of diagnosing chest pain using three "markers of cardiac damage"; and U.S. Patent No. 6,040,147, which refers to a method of characterizing risk in cardiovascular diseases by correlating "a level of a marker of systemic inflammation" to an individual's risk.

The Examiner takes the position that written description is lacking since "the claims are not limited as to the number of markers." Office Action, page 6. To the extent that the argument is due to the use of "comprising" in the claims, which opens the claim to additional biomarkers that can be combined to provide a large number of individual panels, Applicants respectfully submit that this is always true of claims written in "comprising" form, which are construed to include additional unrecited elements or method steps, and so are open to literally an infinite number of theoretical modifications and variations. The use of open language in claims that clearly recite the markers that are required to be measured, as in the present case, is standard and accepted practice (again Applicants refer, only by way of example, to U.S. Patent Nos. 5,604,105 and 6,040,147, which are also written in comprising form, and so presumably optionally include any possible combination of markers) and cannot support a *prima facie* case of a lack of written description.

The Examiner also takes the position that written description is lacking since "the prior art does not teach methods of determining all possible panels to distinguish amongst a plurality of cardiovascular disorders." Office Action, page 6. Applicants question the relevance of a discussion of the teachings of the "prior art" in an analysis of whether or not the present application meets the written description standard. As stated in *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956), "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."

The Examiner also states that, because each biomarker is a unique polypeptide, "any given markers would not be capable of distinguishing 'all cardiovascular disorders.'" Office Action, page 7. Applicants note that the pending claims do not relate to methods that distinguish any and all cardiovascular disorders, and question the relevance of this assertion to a written description analysis of the pending claims. Moreover, the Examiner's argument completely ignores certain known basic biological facts. Of what possible relevance is it that, for example, cardiac troponin, myoglobin, and CK-MB are each a different polypeptide? This is not a meaningful distinction in the context of the present claims, as each "unique polypeptide" is related, not by sequence, but by its indisputable established physiological relationship to myocardial injury. The skilled artisan understands the relationship of these markers to their respective physiological pathways.

The Examiner has acknowledge that the specification provides exemplary data for 9 different marker combinations for distinguishing a plurality of cardiovascular disorders, including myocardial infarction, congestive heart failure, acute coronary syndromes, unstable angina, and pulmonary embolism. Applicants note that these examples include markers selected from each of the classes of markers recited in the present claims, including markers related to blood pressure regulation (*e.g.*, ANP, BNP, and CGRP), markers related to myocardial injury (*e.g.*, cardiac troponin, myoglobin, and CK-MB), markers related to inflammation (e.g., CRP) and markers related to coagulation and hemostasis (*e.g.*, D-dimer). While the Examiner acknowledges sufficient written description insofar as the present application provides actual examples, Applicants respectfully submit that it is not proper to focus the written description analysis on the examples alone, all the while ignoring the rest of the specification. Nor is it the task of the claims to exclude hypothetically inoperable embodiments:

Nor are we concerned that the claims may include inoperable embodiments, as is it

> not a function of the claims to specifically exclude possible inoperative embodiments. Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Geerdes, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974). The Federal Circuit has cautioned against limiting a claimed invention to preferred embodiments or specific examples set forth in the specification. Texas Instruments v. U.S. Int'l Trade Comm., 805 F.2d 1558, 1562, 231 USPQ 833, 835 (Fed. Cir 1986).

Ex Parte Hicks, 2000 WL 33673734, *4 (Bd. Pat. App & Interf.).

Moreover, even if the structure for one or more biomarker was not known, it would be well within the knowledge of the artisan at the time of invention to obtain such information. For example, if a nucleotide sequence for the target gene or a target protein is known or obtained through conventional methods, then one or skill could readily obtain the necessary structural information. Put another way, if the markers are known, as disclosed in the instant specification and further supported by knowledge in the art, or if identifying such structure would be conventional in the art, then there is sufficient written description. This point is clearly articulated by relevant legal precedence as well as in the MPEP:

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. >See also *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005)("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.... As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.").< If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient"). (MPEP § 2163)

In the instant case, the specification discloses various and numerous classes of markers. Furthermore, the instant claims are directed to novel methods for assigning mortality risk based on detection of one or more such markers, which is a contribution over and to the state of the art. As such, if the structural identity of such markers is known or could be readily obtained, then the instant claims have sufficient written description support.

Indeed, the proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date.

See MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* An adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." MPEP § 2163(II)(3)(a).

Applicant respectfully submits that the specification is sufficient to reasonably convey to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. 35 U.S.C. § 112, first paragraph demands no more. In view of the foregoing, Applicant urges the Examiner to withdraw the written description rejection of claims 1-10, 13, and 15-17.

2. Rejection of claims 1-10, 13, and 15-17 under 35 U.S.C. § 112, first paragraph (enablement)

Applicant respectfully traverses the rejection of claims 1-10, 13, and 15-17 as allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

The Examiner acknowledges that the specification is enabling for a method for distinguishing between myocardial infarction and pulmonary embolism using subject-derived markers comprising troponin isoforms, B-type natriuretic peptide, and D-dimer. Office Action, page 7. But the Examiner asserts that the specification does not enable methods to distinguish amongst a plurality of cardiovascular disorders, where the markers used are markers related to blood pressure regulation, myocardial injury, inflammation, and coagulation and hemostasis. Office Action, page 9.

In rejecting the claims, the Examiner seeks to focus the enablement analysis on what is present in specific examples, while ignoring the remaining teachings of the specification. The Federal Circuit has cautioned against limiting a claimed invention to preferred embodiments or specific examples in this manner. See, *Ex Parte Hicks*, 2000 WL 33673734, *4 (Bd. Pat. App & Interf.) (citing *Texas Instruments v. U.S. Int'l Trade Comm.*, 805 F.2d 1558, 1562, 231 USPQ 833, 835 (Fed. Cir 1986)). Moreover, the Examiner approaches the claims as if the skilled artisan knows nothing about the marker types recited in the claims and the specification, or their known relationship to various conditions. *See, e.g.*, Office Action, page 11 ("in order to carry out the claimed invention, one skilled in the art would first need to determine whether any given set of

markers could in fact be used diagnostically"). However, the Examiner does not support the preceding assertion with sufficient scientific or legal reasoning. Contrary to what appears to be the Examiner's personal opinion in this regard, the skilled artisan is well acquainted with diagnostic uses of the markers recited in the claims.

The proper test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, e.g.*, MPEP § 2164.01. As the following analysis demonstrates, the present claims meet this standard.

The factors relevant to an enablement analysis are enumerated in *In re Wands*, so Applicant has attempted to address the Examiner's remarks in the context of the various *Wands* factors.

A. The nature of the invention

The present invention is related to the use of biomarker measurements to diagnose cardiovascular disorders. In particular, claim 1 provides that at least one subject-derived marker related to blood pressure regulation and at least one subject-derived marker related to myocardial injury are used to distinguish between different cardiovascular disorders, for example congestive heart failure and cardiac ischemia and necrosis. In the claimed methods, a subject's risk of having developed or of developing each of a plurality of cardiovascular disorders is based upon the presence or amount of the markers assayed. And in addition to the markers recited in claim 1, other markers such as those related to inflammation and to coagulation and hemostasis can also be included in the claimed methods. *See, e.g.*, Specification, paragraphs [0227]-[0264].

The claimed invention does not relate to the discovery of new markers for use in diagnosing the presence or absence of cardiovascular disorders. Instead, the claimed invention relates to the way in which the markers are used. Specifically, the amount of one or more of the markers assayed is not compared to a predetermined threshold amount, which is traditionally how diagnostic markers are analyzed. To practice the claimed invention, markers may instead be combined into a single composite value that is used as if it were a biomarker itself.

B. The state of the prior art

The general state of the prior art is that biomarkers are routinely used in the art for diagnosis and prognosis of individual cardiac conditions.

As for the specific classes of subject-derived markers recited in claim 1, a review written by Kemp *et al.*, *Br. J. Anaesthesia* 93: 63-73 (2004) notes that the first account of the use of biochemical markers related to myocardial injury was published in 1954, and that the identity and use of a large number of such markers are well known. *See, e.g.*, Kemp *et al.* page 65, Table 2. Likewise, markers related to blood pressure regulation, and in particular natriuretic peptides such as ANP and BNP, and their biosynthetically related fragments such as NT-proANP and NT-proBNP, have found use in the diagnosis of congestive heart failure. *See, e.g.*, Felker *et al., CMAJ* 175: 611-617 for review. With regard to the specific classes of subject-derived markers recited in the dependent claims, markers "related to inflammation" and "related to coagulation and hemostasis" are also well known. *See, e.g.*, Biasucci, *Circulation* 110: e560-e567, 2004, and Fassbender *et al., Stroke* 30: 2101-4 (1999).

The Examiner refers to several publications in an attempt to paint the state of the prior art in a negative light. Notably, none of the cited references appear to be directly related to the claimed invention. Indeed, many of these comments amount to nothing more than generic recitations of difficulties that *might* be encountered in practice in the general use of biomarkers. That type of reasoning is not a sufficient basis for rejecting a claim under the enablement requirement. *See, e.g., In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956), *Ex Parte Hicks*, 2000 WL 33673734 at *3. As discussed below, the Examiner's assertions about the limits of the prior art are not well founded.

For example, the Examiner states that Bast *et al.*, *Clin. Cancer Res.* 11: 6103-8, 2005, "point to the 'lengthy process' of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically." Office Action, page 12. In addition to being merely a recitation of difficulties that *might* be encountered in practice, the Examiner has failed to acknowledge that this "lengthy process" quote, which is found on page 6105, right column, of Bast *et al.*, addresses why some marker tests do not obtain federal regulatory approval. Therefore, with respect to Bast et al. the Examiner's implied assertion of unpredictability is unsupported by any evidence of record, that the claimed methods might not be ready for clinical application. It is not a requirement of the patent laws that a patent application be sufficient to obtain FDA approval, as considerations made by the FDA for approving clinical trials are different from

those made by the PTO in determining whether a claim is enabled. Furthermore, whether or not a claimed invention is ready for clinical application is not a valid basis on which to question the enablement. *See, e.g., Ex Parte Rollins and Stiles*, 2006 WL 2523796 at *5 ("at the risk of being repetitive, evidence that a claimed method was not ready for clinical application is not enough to show nonenablement. What is needed is evidence or sound scientific reasoning that undue experimentation would have been required to carry out the claimed methods).

The Examiner also states that LaBaer, *J. Proteome Res.* 4: 1053-9, 2005, "teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor and also that the process of converting such a biomarker into a practical clinical test is even more daunting." Office Action, page 12. Again, this is nothing more than a recitation of difficulties that *might* be encountered in practice, and that the claimed methods might not be ready for clinical application. More appropriately, the LaBaer publication reflects basic considerations that are routine to one skilled in the field of biomarkers. Moreover, the LaBaer publication does not appear to provide any teachings or statements that are sufficiently directly related to the instantly claimed methods.

The Examiner further attempts to support the rejection (see page 12 of the Office Action) by reference to the following section from Baker, *Nature Biotechnology* 23: 297-304 (2005), page 298:

Walking on Thin Ice

> 'Using a new biomarker is like walking across a frozen lake without knowing how thick the ice is;' says Ole Vesterqvist, director of clinical discovery at NewYork-based Bristol-Myers Squibb. 'You start walking, and you get comfortable. Then you break through.' Vesterqvist describes an example in which published clinical data showed that people with heart failure had higher levels of the peptide endothelin I (ET-1) compared to healthy controls, based on immunoassays. But in studies at Bristol-Myers Squibb, these patients showed no increase in plasma concentration of the peptide, Eventually, Vesterqvist's group found research revealing that the previous studies used an antibody that cross-reacted with the precursor to ET-1, big-ET. Although levels of the precursor are higher in patients with heart failure, the levels of ET-1 are not. Ironically, the Bristol-Myers Squibb assay did not produce the expected results because it was more specific for ET-1 than assays previously used in other laboratories.

The discussion to which the Examiner refers is nothing more than an anecdotal report of a rather simple error on the part of one researcher in one example. To the extent the passage is meaningful at all, it speaks to the need for a rather basic understanding of the biomarker with which one is working. Therefore, it has nothing to do with the claimed invention, except to the extent that it discloses a suitable marker related to blood pressure regulation – big endothelin 1.

Applicants respectfully submit that the state of the prior art is one of common usage of biomarkers generally, and that each of the publications cited by the Examiner are consistent with this understanding. As noted above, the claimed invention does not relate to the discovery of new markers for use in diagnosing the presence or absence of cardiovascular disorders. Instead, the claimed invention relates to the way in which such markers are used.

C. The relative level of skill in the art

The skill in the art is extremely high. The skilled artisan has extensive experience with the clinical use of biomarker tests for diagnosis and prognosis of patients, and also has extensive experience in the generation and characterization of antibodies for use in such tests. As noted above with regard to the state of the art, the articles cited by the Examiner in the rejection emphasize that the skilled artisan is well aware of the potential pitfalls that might be encountered in practice. The artisan is prepared to perform the necessary studies to practice the claimed methods, and understands that the required methods are routine in the art.

D. The quantity of experimentation necessary

As noted above, claim 1 refers to a method of analyzing a subject sample for a plurality of subject-derived markers selected to distinguish amongst a plurality of cardiovascular disorders. According to the claim, at least one subject-derived marker related to blood pressure regulation is used together with at least one subject-derived marker related to myocardial injury. Additional markers from other art-recognized marker classes, for example, subject-derived markers related to coagulation and hemostasis, are referred to in various dependent claims.

The Examiner appears to acknowledge that the specification is enabling for those embodiments specifically exemplified with data (Office Action, page 7). Applicants note that such methods can be practiced on any subject, and can be used to rule in or out (and therefore distinguish between) a plurality of conditions, as required by the claims. Thus, at least with regard to troponin

isoforms, B-type natriuretic peptide, and D-dimer, it appears undisputed that one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The Examiner fails to acknowledge that the skilled artisan can readily extrapolate such exemplary data in the specification regarding specific biomarkers to the general classes of molecules recited in the claims, as each is a representative of an art-recognized class having relationships to well known physiological pathways. Thus, the specification provides examples of how subject-derived markers related to blood pressure regulation (*e.g.*, ANP, BNP) and subject-derived markers related to myocardial injury (*e.g.*, cardiac troponin, myoglobin, CK-MB) may be used to distinguish between different cardiovascular disorders (such as congestive heart failure and cardiac ischemia and necrosis), and how the addition of markers related to coagulation and hemostasis (*e.g.*, D-dimer) can be used to further distinguish additional cardiovascular disorders (such as pulmonary embolism). The exemplary data on molecules such as ANP and BNP can be extrapolated to markers related to blood pressure regulation, data on molecules such as cardiac troponin can be extrapolated to markers related to myocardial injury, data on molecules such as D-dimer can be extrapolated to markers related to coagulation and hemostasis, *etc.*

In contrast to the teachings of the specification and the knowledge in the art, the Examiner appears to approach the claims as if the skilled artisan knows nothing about the marker types recited in the claims and the specification, or their known relationship of such marker types to various conditions. For example, the Examiner offers the conclusory opinion that "in order to carry out the claimed invention, one skilled in the art would first need to determine whether any given set of markers could in fact be used diagnostically." Office Action, page 11. Why? Because of the number of markers? Because each is a different polypeptide? As discussed above with regard to written description, neither of these is a relevant distinction when, for example, both the specification and the prior art teaches that myocardial injury may be identified using any number of cardiac proteins.

In view of the teachings of the specification and the knowledge available in the art, the quantity of experimentation required to practice the invention is no more than routine. The specification provides the artisan with detailed examples of which markers to use and which cardiovascular disorders can be distinguished. It further informs the artisan of suitable methods for each and every step in the process of practicing the claimed methods, from generating antibodies, to

preparing assays, and to selection of subjects and data analysis. When properly considered, it is apparent that what the Examiner likens to "tossing out the mere germ of an idea" or "a general roadmap" (Office Action, page 10) is actually a complete description of how to make and use the claimed invention from start to finish.

Much of the grounds of rejection appear to be directed to the quantity of experimentation necessary. These remarks appear to be based on the Examiner's personal opinion or at most are based on publications which, as discussed above, do not support the Examiner's position on unpredictability in the art as sufficiently related to the instant inventions. The instant specification provides extensive technical discussion and teachings, which allows the artisan to practice the claimed methods without undue experimentation. In sharp contrast, the Examiner has provided insufficient technical evidence or legal reasoning to support the alleged lack of enablement.

For example, the Examiner appears to believe that the claims must enable distinguishing amongst any and all possible cardiovascular disorders using any and all subject-derived markers and any and all sample types in order to satisfy the enablement requirement. Office Action, page 10. Applicants submit that this is not required, either by the claims or by the enablement requirement. Instead, the claims simply relate to distinguishing amongst a plurality of (meaning at least two) cardiovascular disorders. And the combination of at least one marker related to myocardial injury and at least one marker related to blood pressure regulation can distinguish between a plurality of cardiovascular disorders. While it may be theoretically possible that certain unspecified cardiovascular conditions cannot be distinguished by the claimed methods using "all subject-derived markers in all sample types," as the Examiner alleges, this does not negate the fact that the claimed invention can be practiced as written. Moreover, the Board of Patent Appeals and Interferences has repeatedly pointed out in the context of enablement rejections that it is not the task of the claims to exclude potentially inoperable embodiments:

> Nor are we concerned that the claims may include inoperable embodiments, as is it not a function of the claims to specifically exclude possible inoperative embodiments. Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Geerdes, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974).

Ex Parte Hicks, 2000 WL 33673734, *4 (Bd. Pat. App & Interf.).

As discussed above, rather than analyze the claims with knowledge generally available in the art, the Examiner focuses on the number of possible markers in each class. While it may be true that the specification discloses 18 potential "myocardial injury markers" for example, the Examiner does not provide any scientific evidence or reasoned scientific explanation as to why those markers could not each be used in the claimed invention as taught in the specification, and particularly in view of the data regarding cardiac troponin. As stated in MPEP § 2164.04, "it is incumbent on the Patent Office... to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning.... Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." Again, an Examiner's personal opinion is not sufficient.

The Examiner also appears to believe that only "specific markers" (that is, markers that are only affected by a specific disease state) can be used in the claimed methods, or indeed for diagnosis generally; that the skilled artisan would have to perform studies to "weed out" the nonspecific markers present in the various marker classes described in the specification and claims; and that such studies represent undue experimentation. This view is demonstrably incorrect.

For example, the Examiner refers to D-dimer and its use, relative to other markers of coagulation and hemostasis, in distinguishing pulmonary embolism as follows: "markers recited in claim 11 with an exception of D-dimer are not specific markers of pulmonary embolism... and so do not satisfy features of diagnostic markers for pulmonary embolism." *See*, Office Action, page 13. In so stating, the Examiner is apparently unaware that D-dimer itself is not a "specific marker of pulmonary embolism," despite the fact that Applicants have provided evidence that this is indeed the case. *See, e.g.*, Indik and Alpert, *Prog. Cardiovasc. Dis.* 42: 261-272, 2000, page 262 ("Since D-dimer products are produced whenever there is active intravascular thrombosis and fibrinolysis in the body, the specificity of all DD assays is expected to be low"). Nevertheless, it is an FDA-approved test for use in the evaluation of pulmonary embolism, and so presumably does "satisfy features of diagnostic markers for pulmonary embolism," the Examiner's opinion with regard to nonspecific tests notwithstanding.

It must be acknowledged that, as demonstrated by the acceptance of the D-dimer test in the art, even nonspecific markers can be useful clinically when in the hands of the skilled artisan, as the skilled artisan does not use diagnostic tests in an informational vacuum. Rather, diagnostic tests are

used by skilled medical personnel in concert with other available medical indicia related to a subject. As discussed in paragraph [0075] of the present specification, "diagnosis" refers to a relative probability that a certain disease is present in the subject, and not the ability of a "specific marker" to give a definitive yes/no answer to the existence of a disease. Tests can be used to "rule in" a diagnosis, or to "rule out" a diagnosis by signaling an increased or decrease probability of a particular diagnosis. The fact that D-dimer is not specific for pulmonary embolism does not mean that it cannot fulfill its diagnostic role for the skilled artisan.[1]

And again, the Examiner does not provide any scientific evidence or scientifically-based explanation as to why the various markers of coagulation and hemostasis such as are described in the specification and claims could not each be used in the claimed invention as taught in the specification, and particularly in view of the data regarding D-dimer. Indeed, the art teaches that other markers of coagulation and hemostasis may be used in a similar fashion to D-dimer in the evaluation of pulmonary embolism. *See, e.g.*, LeCapra *et al., Blood Coagul. Fibrinolysis* 11: 371-7, 2000; Watanabe et al., Am. J. Hematol. 65: 35-40, 2000.

E. The predictability of the art

In the present case, the methods to be followed are all routine or are described in detail in the specification; the only factor required to practice the claimed invention is the understanding that such methods should be pursued, an issue that is solved by reference to the present specification and claims.

The Examiner's comments in the Office Action regarding the state of the prior art (discussed above) are also relevant to an understanding of the predictability of the art. As discussed in detail above, assertions such as there can be a "lengthy process of assay development," that "many markers that correlate with disease statistically may not prove to be useful clinically," or that "the process of converting such a biomarker into a practical clinical test" amount to broad allegations that the

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[1] In fact, nonspecific tests are used constantly in medicine. Consider the well known "prostate-specific antigen" ("PSA") test. Elevated PSA levels may be caused by conditions including prostate cancer, benign prostate enlargement, inflammation, and infection, and elevations are understood to be affected by both age and race. Despite the fact that only 25 to 30 percent of men who have a biopsy due to elevated PSA levels actually have prostate cancer, the PSA test is routinely used by artisans for initial diagnosis and screening.

disclosure is speculative, coupled with a recitation of difficulties that *might* be encountered in practice. Such reasoning, however, is legally insufficient for rejecting a claim under the enablement requirement.

Applicants respectfully submit that the test of enablement is not whether certain scenarios may be constructed in which the invention might not work, but rather whether one skilled in the art could reasonably make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, e.g.*, MPEP § 2164.01. The present specification and claims meet this standard.

F. The amount of direction or guidance

As the Examiner appears to acknowledge that the specification provides the artisan with several detailed examples of which markers to use for certain exemplary cardiovascular disorders to be distinguished. It further informs the artisan of suitable methods for each and every step in the process of practicing the claimed methods, from generating antibodies, to preparing assays, and to selection of subjects and data analysis. When properly considered, it is apparent that what the Examiner likens the present invention to "tossing out the mere germ of an idea" or "a general roadmap" is actually a complete description of how to make and use the claimed invention from start to finish.

G. The presence or absence of working examples

The Examiner acknowledges that the specification provides exemplary data for various marker combinations "for distinguishing a plurality of cardiovascular disorders, but attempts to minimize the value of these examples by stating the examples "only include MI, congestive [ ] heart failure, acute coronary syndrome, unstable angina, and pulmonary embolism." Office Action, sentence bridging pages 11 and 12. The Examiner also acknowledges that the specification is enabling for a method for distinguishing between myocardial infarction and pulmonary embolism using subject-derived markers comprising troponin isoforms, B-type natriuretic peptide, and D-dimer. Office Action, page 9.

As discussed above, the Examiner seeks to limit the claims by focusing the question of enablement on what is present in the examples, while ignoring the remaining teachings of the

specification. In the context of enablement rejections, the Federal Circuit has cautioned against limiting a claimed invention to preferred embodiments or specific examples set forth in the specification. See, *Ex Parte Hicks*, 2000 WL 33673734, *4 (Bd. Pat. App & Interf.) (citing *Texas Instruments v. U.S. Int'l Trade Comm.*, 805 F.2d 1558, 1562, 231 USPQ 833, 835 (Fed. Cir 1986)).

H. The breadth of the claims

The claims are circumscribed in their breadth, in that they refer to methods for distinguishing amongst a plurality of cardiovascular conditions that rely on measuring subject-derived markers from specified art-recognized classes of biomarkers.

The Examiner's comments concerning the breadth of the claims fail to consider the knowledge available in the art. As noted above, the Examiner appears to believe that the enablement requirement requires the ability to distinguishing amongst any and all possible cardiovascular disorders using any and all subject-derived markers and any and all sample types. The claims, however, only require that the method distinguish between a plurality of cardiovascular disorders using at least one marker related to myocardial injury and at least one marker of blood pressure regulation. The Examiner's focus on the number of subject-derived markers recited in the claims fails consider that the skilled artisan can readily extrapolate the exemplary data in the specification regarding specific biomarkers to the general classes of molecules recited in the claims, as each is a representative of an art-recognized class having relationships to well known physiological pathways.

I. Conclusion

In the present case, the skilled artisan can, by simply following the extensive detailed guidance in the specification, perform the claimed methods using nothing more that routine experimentation. In contrast, the rejection fails to consider the knowledge available in the art, being based on nothing more than broad unsupported allegations that the disclosure is speculative coupled with various difficulties that *might* be encountered in practice. As such, the rejection does not present a sufficient basis for rejecting a claim under the enablement requirement. *See, e.g., In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956), *Ex Parte Hicks*, 2000 WL 33673734 at *3.

Applicants respectfully submit that, when a proper enablement standard is applied, it is apparent that one skilled in the art could reasonably make or use the invention from the disclosures

in the patent coupled with information known in the art without undue experimentation. Because the enablement requirement demands no more, Applicants respectfully request that the rejection be reconsidered and withdrawn.

3. Rejection of claims 1-4, 9-12, 15 and 16 under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1-4, 9-12, 15 and 16 under 35 U.S.C. § 103(a) as being unpatentable over Jackowski, U.S. Patent 5,710,008, in view of Buechler et al., U.S. Patent 5,795,725, Baig, *Am. Heart J.* 135: S216-230, 1998, Kline *et al., Ann. Emerg. Med.* 35: 168-80, 2000, and Zweig *et al., Clin. Chem.* 39: 567-77, 1993.

Claim 1 and its dependent claims all contain the following limitation: that the subject's risk of having developed or of developing each of said plurality of cardiovascular disorders is characterized based upon the presence or amount of the markers measured, wherein the amount of one or more of said markers is not compared to a predetermined threshold amount.

With respect to the underlined limitation, the Examiner relies entirely on the Zweig *et al.* publication, acknowledging that none of the other cited publications disclose or suggest the use of markers without comparison to some predetermined threshold. Zweig *et al.*, however, is not directed to the use of markers for characterizing individual subject's disease risk without comparing markers to a predetermined threshold, as the Examiner asserts. Instead, Zweig *et al.* describes the use of Receiver-Operator Characteristic ("ROC") plots to evaluate the performance of a laboratory test (the ability of the test to discriminate a diseased population from a nondiseased population).

Applicants have previously provided a declaration by Dr. Joseph Anderberg, explaining generally the use of ROC analysis in diagnostic test design, and discussing the teachings of the Zweig *et al.* publication concerning the use of ROC analysis. Dr. Anderberg points out that evaluating the ability of a particular test to discriminate a diseased population from a nondiseased population is a completely different type of analysis, compared to using a test to evaluate the disease state of an individual, which is the subject matter of the present claims. As described in Zweig *et al.*, ROC analysis is used for the former, but not the latter. Thus, ROC analysis can be used to help *guide the selection of a diagnostic threshold*, as discussed beginning on page 571, right column, of Zweig *et al.* But Zweig *et al.* advises that "to use the test for **patient management**, a decision threshold **must** be selected." Page 572, first incomplete paragraph, emphasis added. Dr. Anderberg explains

that Zweig *et al.* does not contemplate the claimed limitation of using a marker value in patient management without comparing to a predetermined threshold, and, in fact, teaches that one cannot do so. Anderberg Declaration, paragraph 8.

The Examiner disagrees with Dr. Anderberg's analysis, stating that the section of Zweig *et al.* entitled "Statistical Comparison of Multiple Tests by use of ROC plots" teaches a "global approach" of comparing entire ROC plots. Office Action, page 48. The Examiner, however, is confusing the comparison of two diagnostic tests relative to one another for their performance and correlation (which is the subject of the section of Zweig *et al.* to which the Examiner refers) with use of diagnostic tests for individual patient management (the subject of the claims). Nothing in this section of Zweig *et al.* has anything whatsoever to do with assigning risk of a disease to an individual subject. As a ROC curve is, by definition, based on measurements from a population of individuals, it is unclear why the Examiner apprehends "comparing entire ROC plots" as related in any way to the subject matter of the present claims. In fact, it is not.

Because the combination of publications cited by the Examiner do not teach or suggest each and every limitation of the claims, and because the cited publications actually teach away from the claimed methods, Applicants respectfully submit that no *prima facie* case of obviousness has been established. In view of the foregoing, request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

4. Rejection of claims 5-8, 13 and 14 under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 5-8, 13 and 14 under 35 U.S.C. § 103(a) as being unpatentable over Jackowski in view of Buechler *et al.*, Baig, Kline *et al.*, and Zweig *et al.*, and in further view of Holvoet *et al.*, U.S. Patent 6,309,888.

As discussed in detail above, the rejection relies on Zweig *et al.* publication as allegedly disclosing the use of diagnostic markers for characterizing individual subject's disease status without comparing markers to a predetermined threshold. In fact, Zweig *et al.* teaches that one cannot do so.

Because the combination of publications cited by the Examiner do not teach or suggest each and every limitation of the claims, and because the cited publications actually teach away from the claimed methods, Applicants respectfully submit that no prima facie case of obviousness has been

established. In view of the foregoing, request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

5. Rejection of claim 17 under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claim 17 under 35 U.S.C. § 103(a) as being unpatentable over Jackowski in view of Buechler *et al.*, Baig, Kline *et al.*, and Zweig *et al.*, and in further view of Heeschan *et al., The Lancet* 354: 1757-62, 1999.

As discussed in detail above, the rejection relies on Zweig *et al.* publication as allegedly disclosing the use of markers for characterizing individual subject's disease status without comparing markers to a predetermined threshold. In fact, Zweig *et al.* teaches that one cannot do so.

Because the combination of publications cited by the Examiner do not teach or suggest each and every limitation of the claims, and because the cited publications actually teach away from the claimed methods, Applicants respectfully submit that no prima facie case of obviousness has been established. In view of the foregoing, request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

6. Obviousness-Type Double Patenting

The Examiner has issued 18 pages of provisional obviousness-type double patenting rejections. In each case, the rejections are improperly founded on the "teachings" of various copending patent applications in combination with various secondary publications. *See, e.g.*, Office Action, page 30, last incomplete paragraph; page 32, first paragraph; page 33, second paragraph; *etc.*

As described in MPEP § 804, any obvious-type double patenting rejection should make clear: (A) the differences between the inventions defined by the conflicting claims - a claim in the patent compared to a claim in the application; and (B) the reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent or copending patent application. As is also noted in MPEP § 804, the disclosure of the patent may not be used as prior art in analyzing claims for obviousness-type double patenting.

Nowhere in the rejections does the Examiner analyze the conflicting claims. Instead, the Examiner appears to have used the various copending patent disclosures as prior art, relying on what

"the co-pending Application teaches." *See, e.g.*, Office Action, page 36. By failing to perform the type of analysis required in any obvious-type double patenting rejection, Applicants have been deprived of a meaningful opportunity to respond to the various rejections. Should the rejections be maintained, Applicant respectfully requests that the correct analysis be presented in a non-final office action, so that Applicants may be afforded an opportunity to reply to the Examiner's comments.

Moreover, each of the double patenting rejections relies on Zweig *et al.* publication as allegedly disclosing the use of diagnostic markers for characterizing individual subject's disease status without comparing markers to a predetermined threshold. In fact, Zweig *et al.* teaches that one cannot do so.

Additionally, no terminal disclaimer is procedurally required in a case where the provisional rejection involves two pending applications and where the rejection is the sole remaining issue in the case. See MPEP 804 (I)(B) (The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.") In the event that other rejections of the present claims are successfully overcome by the current communication, withdrawal of the instant provisional rejections would be appropriate. Applicants authorize the examiner to follow MPEP 804 (I)(B) and allow the case without issuing a further Office Action should the provisional obviousness type-double patenting rejection be the sole remaining issue in the case.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Furthermore, should any matters remain outstanding it should be noted that a notice of appeal has been filed concurrent to this submission, along with a request for a pre-appeal brief conference.

FEE AUTHORIZATION

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. **23-2415** (Docket No. 36671-745.502).

Respectfully submitted,
WILSON SONSINI GOODRICH & ROSATI

Date: February 29, 2008

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